

### **REMARKS /ARGUMENTS**

Claims 1, 3, 5, 7, 9, 12-15, 18, 20, 24, 49, 50, 51, 55, 56, 60, 61, 112 remain in the application. Claim 111 has been canceled, and claims 1, 3, 5, 7, 9, 12-15, 18, 20, 24, 49, 50, 51, 55, 56, 60, 61, and 112 have been amended, without prejudice or disclaimer of any previously claimed subject matter. Claims 2, 4, 6, 8, 10, 11, 16, 17, 19, 21-23, 25-48, 52-54, 57-59, 62-110 and 113-120 have been withdrawn by the Examiner. Claims 121-154 have been added. Support for the amendment appears in the specification e.g., on pages 11, 12, 27 and 28.

#### **Double Patenting**

Claims 1, 3, 5, 7, 9, 12-15, 18, 20, 24, 49-51, 55, 56, 60, and 61 stand provisionally rejected under the judicially created doctrine of double patenting over claims 1-28 of copending Application No. 10/027, 593. If the rejection is maintained, Applicant will submit a Terminal Disclaimer upon indication of allowable subject matter.

#### **Rejection under 25. U.S.C. § 112**

The Examiner suggests that the term "residue" renders the scope of the instant claims unclear. Applicant respectfully traverses this objection.

The term "residue" is defined on pages 9-10 of the specification. One of ordinary skill in the art could easily ascertain the metes and bounds of the presently claimed invention in light of the specification and knowledge in the art. "Residue," as recited in the claims, refers to a radical of a compound having an open valence. For example, any synthetically feasible atom or atoms of the compound of formula I can be removed to provide the open valence, provided the resulting compound is able to localize in or near a tumor. Based on the linkage that is desired, one skilled in the art can select suitably functionalized starting materials that can be derived from a compound or formula I using procedures that are known in the art. Page 9 of the specification discloses non-limiting examples of suitable atoms that can be removed, which includes the NH<sub>2</sub> group of the a-carboxamide, the NH<sub>2</sub> group of the b-carboxamide, the NH<sub>2</sub> group of the d-carboxamide, the NH<sub>2</sub> group of the e-carboxamide, the hydrogen atom of the CH<sub>2</sub>OH group at the 5'-position of the sugar ring, and the X at the 6-position. The claims are clear in view of the

specification and knowledge in the art. Thus, Applicant respectfully requests withdrawal of this rejection.

**Rejections under 35 U.S.C. § 102**

Claims 1, 3, 5, 12,13, 15,18, 20, 24, 49-51, 55, 56, 111-112 are rejected under 35 U.S.C. § 102(b) as anticipated by Russell-Jones *et al.* U.S. Patent 5,428,023 (Russell-Jones I).

Claims 1, 3, 5, 7, 9, 12-13, 15, 18, 20, 24, 49-51, 55, 56, 61 and 111-112 are rejected under 35 U.S.C. § 102(b) as anticipated by Russell-Jones *et al.*, *Bioconjugate Chem* 1995 6, 459-465 (Russell-Jones II) or U.S. Patent No. 5,548,064 (Russell-Jones III).

Russell-Jones I discloses orally administered complexes of vitamin B12. Russell-Jones I is directed to providing systems and methods of oral delivery to the intestine. See, e.g., col. 1, lines 15-30. Russell-Jones I is directed toward the goal of solving problems associated with oral delivery, and states at col. 2, lines 14-18 that the object of the invention is to use the vitamin B12 uptake mechanism to transport substances from the intestinal lumen to the circulation.

In contrast, the amended claims are directed to compositions suitable for intravenous administration, which are not disclosed or suggested in Russell-Jones I. Russell-Jones I does not disclose the compositions comprising the compounds recited in claim 1 and the other independent claims. Further, Russell-Jones I does not disclose the specific embodiments recited in the dependent claims, including complexes of chemotherapeutic agents linked to specific carboxamide positions of the compound of formula I, and complexes including the specifically claimed chemotherapeutic agents. Russell-Jones does not disclose chemotherapeutic use of the compounds, and does not disclose the chemotherapeutic agents specifically recited in the claims. Thus, Russell-Jones I fails to disclose the compositions defined by the amended claims.

Similarly, Russell-Jones II does not identically disclose the compositions defined by the amended claims that are suitable for intravenous administration. Russell-Jones II relates to Vitamin B12 mediated oral delivery systems for granulocyte-colony stimulating factor (G-CSF) and erythropoietin (EPO). Russell-Jones II discloses that the goal was to develop orally active EPO and G-CSF that could pass through the epithelium of the gastrointestinal tract. This was

done to overcome the need for parenteral administration (page 459 col. 1 of Russell-Jones II). Thus, Russell-Jones II provides no disclosure of, or desirability to make, compositions that are suitable for oral administration. Moreover, Russell-Jones II does not disclose the specific embodiments defined by the dependent claims, including the specific linkages, linkers and chemotherapeutic agents recited in the claims, or complexes for chemotherapeutic use.

Russell-Jones III also does not identically disclose the compositions suitable for intravenous administration defined by the amended claims. Russell-Jones III discloses complexes of vitamin B12 (VB12) and GCSF or EPO. Russell-Jones III does not disclose the claimed compositions for intravenous administration comprising a residue of a compound of formula I linked to a residue of one or more chemotherapeutic agents. Russell-Jones III does not disclose or suggest compositions for administration intravenously, or linkage to chemotherapeutic agents as recited in the claims.

Claims 1, 3, 5, 7, 9, 12-13, 15, 18, 20, 24, 49-51, 55, 56, 60, 61, 111 and 112 are rejected under 35 U.S.C. § 102(b) as anticipated by Pathare *et al.*, Bioconjugate Chem. 1996, 7, 217-232.

Pathare *et al.* discloses the synthesis of cobalamin-biotin conjugates. Pathare *et al.* does not disclose the compositions recited in the claims that are suitable for intravenous administration and comprise a residue of a compound of formula I linked to a residue of a chemotherapeutic agent in a pharmaceutically acceptable carrier. Pathare *et al.* does not disclose compositions for intravenous administration, or the chemotherapeutic agents recited in the claims or the other embodiment recited in the dependent claims. There is no disclosure in Pathare *et al.* of the compositions defined by the specific limitations of the claims.

In view of the above arguments, Applicant requests that the rejections under § 102 be withdrawn.

**Rejections under 35 U.S.C. § 103(a)**

Claims 1, 3, 5, 7, 9, 12-15, 18, 20, 24, 49-51, 55, 56, 60, 61, 111, and 112 are rejected under 35 U.S.C. § 103(a) as being obvious over Pathare *et al.*, Bioconjugate Chem. 1996, 7, 217-232, in view of Grissom *et al.*, U.S. Patent No. 6,315,978.

Pathare *et al.*, as noted above, discloses the synthesis of cobalamin-biotin conjugates. Pathare *et al.* does not disclose the compositions recited in the claims that are suitable for intravenous administration and comprise a residue of a compound of formula I linked to a residue of a chemotherapeutic agent in a pharmaceutically acceptable carrier. Pathare *et al.* does not suggest the compositions defined by the claims, either alone or in combination with Grissom *et al.* Grissom *et al.* discloses vitamin B12 conjugates wherein the bioactive agent is conjugated to the cobalt atom. Grissom does not teach or suggest the claimed compositions, and provides no further motivation in view of Pathare *et al.* to make the claimed compositions.

There is no motivation in Pathare *et al.*, alone or in combination with Grissom to make the claimed compositions. The disclosure of Pathare *et al.* is limited to several cobalamin-biotin complexes. There is no suggestion of the specific compounds recited in the claims, or of the specific linkages and chemotherapeutic agents in the claims. There is no teaching or suggestion of intravenous formulation. No motivation to make the claimed compositions exists in Pathare *et al.*, and the disclosure of Grissom does not provide any further motivation for one of ordinary skill in the art to make the specific compositions recited in the claims.

Accordingly, withdrawal of this rejection is respectfully requested.

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### Conclusion

Allowance of the claims as amended herein is respectfully requested.

The Commissioner is authorized to charge any fees not provided herewith, or credit any overpayment associated with this filing to Deposit Account 11-0980.

Respectfully submitted,

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